Second-line treatment options in advanced non-small cell lung cancer

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Introduction

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related death in both men and women in most of the Western world, with an estimated 900,000 deaths per year worldwide [1]. Most patients (approximately 80%), present with locally advanced stage III or metastatic stage IV NSCLC and are ineligible for curative surgery [2,3]. The long-term prognosis for patients with NSCLC remains poor, with the 5-year survival rate ranging from 8% to 15% [4].

Chemotherapy with cisplatin-based regimens was shown to prolong survival, relieve symptoms in most cases, and to improve quality of life. The introduction of several new agents, including paclitaxel, gemcitabine, and vinorelbine, offered hope for a better outcome because overall survival improved with combination regimens that included these new agents compared with cisplatin alone [5]. The addition of bevacizumab to platinum doublets has added an additional two months of survival time compared with chemotherapy alone [6].

Based on the results of a randomised phase III trial comparing cisplatin plus pemetrexed to cisplatin plus gemcitabine in the first-line setting [7], pemetrexed was approved by both the European Medicinal Evaluation Agency (EMEA) and the FDA, in combination with cisplatin, as first-line treatment for patients with non-squamous NSCLC.

Despite these favourable results, most patients receiving front-line chemotherapy experience disease progression. Patients who experience disease progression during or after first-line treatment for advanced NSCLC have a limited life expectancy [8]. The aims of second-line treatment should be palliation of symptoms, benefit in quality of life, and prolongation of survival. Even so, the impact of treatment on the natural history of the disease is modest. As shown in a recent review of 19 phase III trials [9], in the second-line or later setting, the median objective response rate was 6.8%, and median overall survival was 6.6 months.

The 1997 guideline of the American Society of Clinical Oncology (ASCO) stated that "there is no current evidence that either confirms or refutes that second-line chemotherapy improves survival in patients with advanced NSCLC" [10].

In recent years, the efficacy of several drugs in the second-line setting has been demonstrated in phase III trials, and now second-line treatment can be considered a standard of care [11].

In first-line treatment of patients with good performance status (PS), doublet chemotherapy has been shown to be more effective than single-agent therapy, both in terms of response and survival [12]. Actually, in patients with NSCLC progressing after first-line chemotherapy, the use of monochemotherapy is necessary, as combination chemotherapy results in increased toxicity without any survival advantage [13–16].

In 2009 Di Maio and colleagues [17] presented a meta-analysis based on individual patient data. The main objective was to compare the efficacy of doublet chemotherapy with single-agent treatment for the second-line treatment of advanced NSCLC. Eight eligible trials were identified. OS was not significantly different between arms ($P = 0.32$). Median OS was 37.3 and 34.7 weeks in the doublet and single-agent arms, respectively. Hazard ratio (HR) was 0.92 (95% confidence interval [CI], 0.79 to 1.08). Response rate was 15.1% with a doublet and 7.3% with a single agent ($P = 0.0004$). Median progression-free survival was 14 weeks for doublet and 11.7 weeks for single-agent treatment ($P = 0.0009$; HR 0.79; 95% CI, 0.68 to 0.91). Patients treated with doublet chemotherapy had significantly more grade 3–4 haematologic (41% *versus* 25%; $P = 0.0001$) and grade 3–4 non-haematologic toxicity (28% *versus* 22%; $P = 0.034$). In conclusion, randomised evidence available for this individual patient data meta-analysis does not support the use of combination chemotherapy as second-line treatment for patients with NSCLC, based on an increase in toxicity without any gain in survival.

In the USA and Europe, the current options for the second- and third-line treatment of advanced NSCLC are cytotoxic drugs (pemetrexed, docetaxel) and targeted agents (erlotinib, gefitinib) [18,19].

In this review, we evaluate the available evidence and explore the role and importance of second-line treatment options in advanced NSCLC, with the aim of optimising treatment selection.

Chemotherapy

Docetaxel

Two phase III trials demonstrated that docetaxel can produce longer survival and better quality of life than best supportive care (BSC) alone [20] and single-agent chemotherapy [21]. In 2000, the results of these studies allowed the registration of docetaxel in the USA and Europe (75 mg/m^2 every 3 weeks) as the first cytotoxic agent for the second-line treatment of NSCLC.

The TAX 317 study [20] established docetaxel as superior to best supportive care with respect to survival, and also showed that quality of life was improved with active therapy [22]. The study randomised patients to docetaxel, evenly divided between doses of 75 mg/m^2 and 100 mg/m^2 on a 3-weekly regimen, *versus* best supportive care in the control arm. Only the 75 mg/m^2 dose was found to improve survival, with a median survival of 7.5 months compared to 4.6 months on best supportive care ($P = 0.010$), though with a median survival in the higher-dose arm of 5.9 months. This was thought to reflect some contribution from toxicity, with 85.7% of patients in the 100 mg/m^2 arm experiencing grade 3 or 4 neutropenia compared with 67.3% in the 75 mg/m^2 arm. Notably, 11 patients (22.4%) in the 100 mg/m^2 arm developed febrile neutropenia, 3 of whom died, as compared with just one case (1.8%) of non-fatal febrile neutropenia in the 75 mg/m^2 arm. The improvement in quality of life was demonstrated by a statistically significant difference in a pain scale in patients treated with docetaxel ($P = 0.006$), with trends toward less fatigue ($P = 0.06$) and weight loss ($P = 0.07$). Additionally, significantly less tumour-related medication was used in the docetaxel patients ($P = 0.02$) [22].

The first phase III trial to show the superiority of docetaxel over another agent was TAX 320 [21], in which docetaxel (at 75 mg/m^2 and 100 mg/m^2) was compared to the investigator's choice of vinorelbine or ifosfamide. Both doses of docetaxel showed greater response, although as in TAX 317, only docetaxel 75 mg/m^2 showed a statistically significant improvement in 1-year survival of 32%, compared to 19% in the control arm ($P = 0.025$), with survival in the 100 mg/m^2 group only 21%. There was again a large difference between grade 4 neutropenia incidence in the two arms, with 77% of patients in the 100 mg/m^2 arm *versus* 54% in the 75 mg/m^2 arm developing this toxicity.

In 2004 a phase II randomised trial [23] confirmed that docetaxel at a dose of 75 mg/m^2 has a more favourable toxicity profile than, and a similar efficacy to, docetaxel at 100 mg/m^2. The current problem of this treatment remains haematologic toxicity.

Docetaxel as single agent dosed weekly

In order to reduce the haematologic toxicity of docetaxel from that seen with 75 mg/m^2 given every 3 weeks, several clinical trials have explored weekly administration of the drug.

In terms of second-line treatment, following a randomised phase II study [24] with safety as a primary endpoint, a weekly docetaxel schedule was compared with the standard schedule in three phase III trials. In a Spanish study [25], more than 250 patients were randomised between 3-weekly and weekly docetaxel (36 mg/m^2 for 6 weeks every 2 months). The results did not demonstrate significant differences between 3-weekly and weekly docetaxel in either the 1-year survival rate or median survival time (27% *versus* 22% and 6.6 *versus* 5.4 months, respectively; $P = 0.076$), but an advantage was seen with the weekly schedule in terms of febrile neutropenia (7.8% *versus* 0.8%; $P = 0.01$), although it was associated with significantly higher incidences of anaemia ($P = 0.011$), diarrhoea ($P < 0.05$), and grade 3–4 mucositis ($P = 0.032$).

In a German study [26], 208 patients were randomised to receive 3-weekly or weekly docetaxel (35 mg/m^2 for 3 weeks every 28 days), and the primary endpoint was overall survival. A significantly lower rate of haematologic toxicity was recorded for the weekly arm (20.6% *versus* 4.8% patients suffered from neutropenia), with a significant difference observed in the median survival time and 1-year survival rate for the two schedules (6.3 *versus* 9.2 months and 26.9% *versus* 39.5% in the 3-weekly and weekly treatment groups, respectively; $P = 0.07$).

Finally, an Italian study [27] investigated a possible advantage in terms of quality of life using weekly docetaxel (33.3 mg/m^2 for 6 weeks every 2 months) *versus* 3-weekly docetaxel in patients with recurrent NSCLC. No difference was found in the global quality-of-life score at 3 weeks. The median

survival times were 29 and 25 weeks in the 3-weekly docetaxel and weekly docetaxel arms, respectively. There was insufficient statistical power to detect clinically relevant differences in overall survival.

Two meta-analyses [28,29] were recently performed that included these previous randomised trials in order to evaluate whether weekly docetaxel can result in longer survival than with the standard 3-weekly schedule in previously treated advanced NSCLC patients.

In the first meta-analysis [28], a significantly lower incidence of grade 3–4 neutropenia for weekly docetaxel was found (relative risk [RR], 0.22; 95% CI, 0.19–0.42; $P < 0.0001$). This advantage translates into an absolute benefit of 15–19%, with nine patients needing to be treated for one to receive a benefit. When considering only the phase III randomised trials (682 patients), overall survival did not differ significantly between the two regimens (RR, 1.01; 95% CI, 0.76–1.42; $P = 0.785$).

The second meta-analysis, recently published [29], is based on updated individual patient data from 865 patients enrolled in three phase III and two phase II randomised trials.The results show no significant difference in efficacy between weekly docetaxel and 3-weekly docetaxel as second-line treatment in advanced NSCLC patients (median survival time, 26.1 *versus* 27.4 weeks, respectively; HR 1.09; 95% CI, 0.94–1.26; $P = 0.245$). The risk for febrile neutropenia was significantly lower with the weekly schedule. The authors concluded that weekly docetaxel represents a valid alternative for all patients with NSCLC suitable for second-line chemotherapy, based on a better toxicity profile and no relevant differences in survival.

Actually the use of a weekly docetaxel schedule for relapsed NSCLC patients is not supported by a direct comparison with pemetrexed.

Collectively these results suggest that weekly dosing is an acceptable alternative, particularly in a patient at greater baseline risk for neutropenia. However, it is important to note that the weekly docetaxel dose and schedule have not been approved by regulatory authorities in the USA or Europe.

Pemetrexed

Pemetrexed received in 2003 FDA approval for malignant pleural mesothelioma, based on a randomised, phase III, single blind, multicentre trial that compared cisplatin alone *versus* cisplatin plus pemetrexed [30]. The patients (n = 448) were randomised to receive pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 or cisplatin alone at the same dose. The study demonstrated that pemetrexed significantly improves survival by 3 months when administered with cisplatin, with a significant difference in overall response rate (41.3% *versus* 16.7% in pemetrexed/cisplatin arm and cisplatin alone arm, $P < 0.0001$).

Pemetrexed was approved in 2004 as second-line therapy in patients with previously chemotherapy-treated advanced NSCLC based on a randomised, open-label, phase III trial [31]. In a randomised phase III trial, 571 NSCLC patients previously treated with a platinum-based therapy were randomly assigned to receive a monotherapy with pemetrexed (283 patients), at the dose of 500 mg/m^2 on day 1 of a 3-week schedule or docetaxel (288 patients), administered at the dose of 75 mg/m^2 on day 1, every 3 weeks. Response rates were 9.1% and 8.8% for pemetrexed and docetaxel, respectively. Median progression-free survival was 2.9 months for each arm, and median survival time was 8.3 months *versus* 7.9 months, respectively. The 1-year survival rate for each arm was 29.7%. Patients receiving docetaxel were more likely to have grade 3 or 4 neutropenia (40.2% *versus* 5.3%; $P = 0.001$), febrile neutropenia (12.7% *versus* 1.9%; $P = 0.001$), neutropenia with infections (3.3% *versus* 0.0%; $P = 0.004$), hospitalisations for neutropenic fever (13.4% *versus* 1.5%; $P = 0.001$), hospitalisations due to other drug-related adverse events (10.5% *versus* 6.4%; $P = 0.092$), use of granulocyte colony stimulating factor support (19.2% *versus* 2.6%; $P = 0.001$) and all-grade alopecia (37.7% *versus* 6.4%; $P = 0.001$) compared with patients receiving pemetrexed. Overall, the trial showed that pemetrexed and docetaxel had comparable activity and efficacy, but pemetrexed was associated with significantly less haematological toxicity and alopecia.

A multivariate analysis conducted with data from early-phase pemetrexed trials established an association between an increased risk of severe pemetrexed-related toxicity and elevated serum homocysteine and/or elevated methylmalonic acid [32]. Thus, since December 1999, folic acid and vitamin B12 supplementation has been included in all pemetrexed-based regimens. The standard vitamin supplementation included oral folic acid (350–1000 μg) daily and a vitamin B12 injection (1000 μg) every 9 weeks, beginning 1–2 weeks before the first dose of pemetrexed and continuing until 3 weeks after the last dose of pemetrexed in the treatment.

Based on these considerations, two randomised trials investigated the efficacy of a higher dose of pemetrexed given with vitamin supplementation. A phase III randomised trial compared pemetrexed at

a dose of 500 mg/m^2 with a dose of 900 mg/m^2, as second-line therapy in NSCLC patients [33]. The primary endpoint was overall survival. No statistical difference was observed between the treatment arms. In fact, median survival (6.7 months *versus* 6.9 months, HR 1.0132; 95% , 0.837–1.226), progression-free survival (2.6 months *versus* 2.8 months, HR 0.9681; 95% CI, 0.817–1.147), and response rate (7.1% *versus* 4.3%; $P = 0.1616$), were similar between lower (288 patients) *versus* higher dose (291 patients) of pemetrexed.

Another phase II randomised trial [34] compared the standard dose of pemetrexed with a higher dose of 1000 mg/m^2. Response rates were 18.5% (90% CI, 12.6–25.8%) and 14.8% (90% CI, 9.5–21.6%), median survival times were 16.0 and 12.6 months, 1-year survival rates were 59.2% and 53.7%.

Drug-related toxicity was generally tolerable for both doses; however, the safety profile of the standard dose showed generally milder toxicity. Overall, these two trials confirmed the pemetrexed dose of 500 mg/m^2 as the standard for second-line therapy in pretreated NSCLC patients, and reported that dose intensification is not always accompanied by higher efficacy.

At ASCO 2010, Vanvakas presented a randomised phase III trial [35] comparing pemetrexed with erlotinib in pretreated patients with advanced NSCLC. There was no difference in terms of objective response rate (11.6% *versus* 6.8%; $P = 0.166$), median TTP (2.9 *versus* 3.6 months; $P = 0.434$) and median OS (8.9 *versus* 7.7 months; $P = 0.528$) between the pemetrexed and erlotinib arms, respectively. The disease control rate (DCR) was 34.1% in the pemetrexed and 24.7% in the erlotinib arm ($P = 0.082$). The incidence of recurrences was significantly higher in the erlotinib (91.3%) than in the pemetrexed (78.9%) arm ($P = 0.003$). There was more grade 3–4 haematologic (neutropenia and thrombocytopenia) toxicity in the pemetrexed arm and skin rash in the erlotinib arm. The authors concluded that pemetrexed and erlotinib have a good toxicity profile and demonstrated a comparable efficacy as salvage treatment in patients with advanced NSCLC.

The importance of histology in testing the efficacy of pemetrexed

The importance of NSCLC histology in testing the efficacy of pemetrexed was first reported by a retrospective analysis from the second-line registration trial [31].

In fact, in this study, significant treatment-by-histology interactions for both median survival ($P = 0.001$) and progression-free survival ($P = 0.004$) indicated greater efficacy for non-squamous patients treated with pemetrexed. Non-squamous patients had a longer overall survival time on pemetrexed than on docetaxel (9.3 months *versus* 8.0 months, respectively; HR 0.78; 95% CI, 0.61–1.00; $P = 0.047$), whereas squamous patients had a shorter overall survival time on pemetrexed than on docetaxel (6.2 months *versus* 7.4 months, respectively; HR 1.56; 95% CI, 1.08–2.26; $P = 0.018$). Moreover, non-squamous patients had a little longer progression-free survival time on pemetrexed than on docetaxel (3.1 months *versus* 3.0 months, respectively; HR 0.82; 95% CI, 0.66–1.02; $P = 0.076$), while squamous patients had a little shorter progression-free survival time on pemetrexed than on docetaxel (2.3 months *versus* 2.7 months, respectively; HR 1.40; 95% CI, 1.01–1.96; $P = 0.046$). While the efficacy of pemetrexed differed by histologic type, the efficacy of docetaxel did not. Higher response rates occurred in the pemetrexed arm compared to the docetaxel arm in patients with adenocarcinoma (12.8% *versus* 9.9%) or large cell carcinoma (12.5% *versus* 3.7%), whereas response rates for patients with squamous cell carcinoma (2.8% *versus* 8.1%) or other NSCLC tumours (3.7% *versus* 10.0%) favoured docetaxel [36,37].

In 2003 Sigmund had demonstrated that patients with high levels of thymidylate synthase (TS) expression, such as those with squamous carcinoma, are less sensitive to pemetrexed [38]. In 2006 Ceppi [39] reported that squamous-cell and high-grade carcinoma are related with higher TS expression levels, which should be considered when treating patients with TS-inhibiting agents.

A recent review from Hirsch and colleagues [40] considered the prognostic and predictive role of histology in advanced NSCLC. The authors identified publications detailing phase II or III studies, retrospective analyses, and meta-analyses that reported a statistically significant prognostic or predictive role for histology. Although there were differences in study design and analyses, evidence suggests that histology may be prognostic or predictive of clinical efficacy outcomes.

A second phase III [41] study of pemetrexed in NSCLC reported non-inferior efficacy and better tolerability for cisplatin plus pemetrexed than for cisplatin plus gemcitabine in the frontline setting. This phase III study identified a significant treatment-by histology interaction for pemetrexed. As a result of this study, pemetrexed was recently approved in Europe,

Canada, and the USA in combination with cisplatin for the front-line treatment of nonsquamous NSCLC.

In 2009 a review was published [42] the examined the differential efficacy of pemetrexed according to histology in two large, phase III NSCLC trials [31–34,36–41]. The authors suggested pemetrexed should not be recommended for the treatment of squamous cell carcinoma, but, because of efficacy and safety advantages, pemetrexed may be preferable to other agents for treatment of patients with non-squamous NSCLC.

Epidermal growth factor receptor inhibitors

Erlotinib

Erlotinib is a HER1/EGFR tyrosine kinase inhibitor. Erlotinib monotherapy is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. Erlotinib was approved by the FDA in November 2004, and by the EMEA in October 2005.

The BR.21 study was a phase III randomised double-blind placebo-controlled trial assessing the efficacy of erlotinib treatment of patients with advanced and chemotherapy-refractory NSCLC [43].

A total of 731 patients were randomly assigned in a 2:1 ratio to receive erlotinib or placebo. At the time of the study, pemetrexed was not available, and there was concern about the toxicity and effectiveness of further chemotherapy after failure of standard chemotherapy in some patients, therefore it was reasonable to compare erlotinib with placebo. The primary endpoint of the study was overall survival. Response rate was 8.9% in the erlonitib group, and less than 1% in the placebo group; median response duration was 7.9 months and 3.7 months, respectively. Median survival was 6.7 months with erlotinib and 4.7 months with placebo ($P < 0.001$). One-year survival was 31% with erlotinib and 21% with placebo. The objective responses (OR) were more frequent in women (14% *versus* 6%; $P < 0.0065$), in patients with adenocarcinoma, as compared with other histotypes (14% *versus* 4.1%; $P < 0.0001$), and in patients without a smoking history (25% *versus* 4%; $P < 0.0001$). The BR.21 study was the first clinical trial in which a novel targeted agent, such as erlotinib, significantly improved survival in chemotherapy-refractory advanced NSCLC patients (Fig. 1).

As expected, the most common toxicities seen in this trial were diarrhoea and rash as was seen in the previous studies. Dose reductions were carried out in 12% of patients due to rash and in 5% for diarrhoea. Erlotinib was discontinued only in 5% of patients due to toxicity. In contrast to most cytotoxic agents, grade 3 or 4 neutropenia was not reported with erlotinib. In the BR.21 study, pulmonary infiltrates and pneumonitis (3%) were seen equally in the erlotinib *versus* placebo arm. One patient died on each arm due to pneumonitis which was most likely related to the underlying lung cancer and not the drug. The quality-of-life analysis supports the true palliative benefit of erlotinib [44].

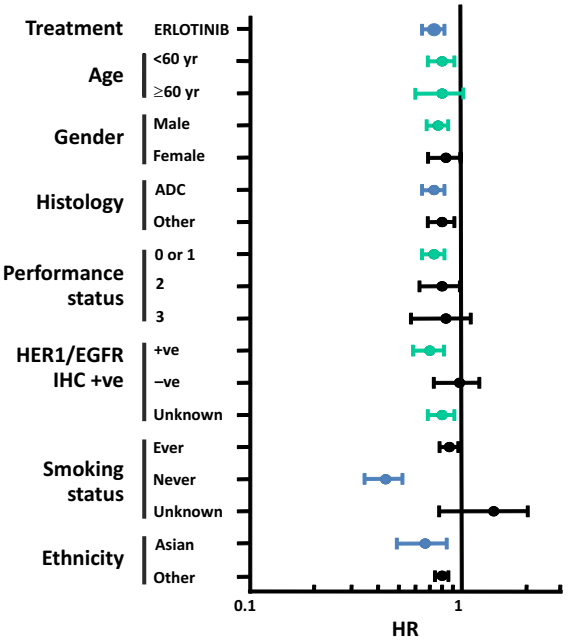

Fig. 1. Analysis of prognostic factors influencing survival in the BR.21 trial [43].

TRUST (Tarceva Survival Lung Cancer Treatment) study is an open-label, non-randomised, multicentre, phase IV trial in patients with advanced NSCLC who have failed standard chemotherapy or cannot receive other systemic anticancer therapy or are not medically suitable for chemotherapy or are ineligible for other clinical trials with erlotinib. The trial was designed to allow access to erlotinib monotherapy for suitable patients in countries where the drug had not been licensed yet. Almost 7,000 patients have been enrolled into the TRUST study at 549 centres in 52 countries worldwide [45].

Recently Tiseo and colleagues reported the interim analysis from the Italian experience [46]. At time of this analysis, data from 651 patients were available. Erlotinib was administered as first-, second-, third- or other-line. Response rate was 9%, with a disease-control rate of 63%. Median PFS was 15 weeks,

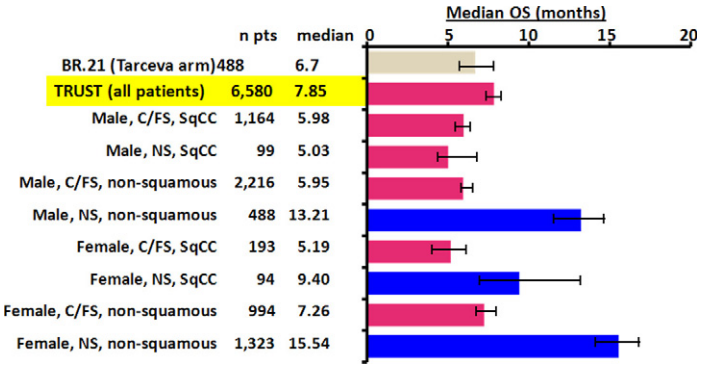

Fig. 2. Median overall survival in the TRUST trial considering different clinical subgroups of patients [47]. NS: non smoker; C/FS: current/former smoker; SaCC: squamous histology.

and was longer in females ($P < 0.001$), patients with adenocarcinoma ($P = 0.008$), those with no smoking history ($P < 0.001$) and patients who experienced skin toxicity ($P < 0.001$). Safety data were available for 609 patients, 35% of whom had at least one adverse event (AE), but only 4% of patients discontinued treatment due to erlotinib-related AEs.

In 2010 Reck [47] published phase IV data. The disease control rate was 69% in 5,394 patients for whom best response data were available. Survival data were available for 6,580 patients. Median progression-free and overall survival times were 3.25 months and 7.9 months, respectively (Fig. 2). The 1-year survival rate was 37.7%. Among the 6,580 patients included in the safety analysis, 799 (12%) experienced one or more erlotinib-related adverse events (AEs), and only 4% experienced an erlotinib-related serious AE. Of the 6,580 patients for whom data were available, dose reductions were reported in 1096 (17%), the majority (95%) due to an erlotinib-related AE (most commonly rash 65% or diarrhoea 10%). Treatment was discontinued for 337 patients (5%) because of erlotinib-related AEs.

With respect to the question whether chemotherapy is superior to therapy with TKIs in second line in wild-type patients, actually we can only indirectly compare the results from the registrative studies among them. This comparison does not indicate a better efficacy for chemotherapy, but the TKIs clearly have a better toxicity profile (Tables 1, 2).

Recently the data of the TITAN study (Tarceva in Treatment of Advanced NSCLC), a randomised,

Table 1
Indirect comparison of selected grade 3 or 4 toxicities using registered second-line agents [31,43]

Toxicity	Percentage of patients		
	Pemetrexed [31]	Docetaxel [31]	Erlotinib [43]
Non-haematologic toxicities			
Fatigue	5.3	5.4	19
Nausea	2.6	1.8	3
Vomiting	1.5	1.1	3
Diarrhoea	0.4	2.5	6
Neurosensory	0	1.1	0
Rash	0.8	0.7	9
Alopecia (any grade)	6.4	37.7	0
Haematologic toxicities			
Neutropenia	5.3	40.2	0
Anaemia	4.2	4.3	0
Thrombocytopenia	1.9	0.4	0
Febrile neutropenia	1.9	12.7	0

Table 2
Indirect comparison of efficacy using registered second-line agents [31,43]

	Docetaxel (N = 288)	Pemetrexed (N = 283)	Erlotinib[a] (N = 488)
Response rate (%)	9.1	8.8	8.9
Progression-free survival (months)	2.9	2.9	2.2[b]
1-year survival (%)	29.7	29.7	31.2
Median survival in PS 0/1 pts (months)	9.1	9.4	9.4

[a] Patient in 2nd–3rd line.
[b] PS = 0–2.

open-label study, have been presented at the European Multidisciplinary Conference in Thoracic Oncology (EMCTO) 2011.

The SATURN study [48] (Sequential Tarceva in Unresectable NSCLC) was designed to test erlotinib as a maintenance therapy *versus* placebo in patients who had shown a response or stable disease after four cycles of first-line chemotherapy. The significant fraction of patients who progressed by the time of the repeat imaging after four cycles of first-line platinum-based doublet chemotherapy was directed to the TITAN trial, which was a head-to-head comparison of erlotinib *versus* either docetaxel or pemetrexed, both well studied and commonly used second-line agents for advanced NSCLC. TITAN was closed prematurely due to slow recruitment.

For the primary endpoint of overall survival (OS), there was no significant difference between erlotinib *versus* chemotherapy (HR 0.96; 95% CI, 0.78–1.19; $P = 0.7299$). Similarly, in subgroup analyses, there were no significant differences across any of the clinical subgroups examined. For OS according to epidermal growth factor receptor (*EGFR*) mutation status, there was an indication of improved OS with confirmed *EGFR* wild-type for erlotinib *versus* chemotherapy (6.6 *versus* 4.4 months; HR 0.85; 95% CI, 0.59–1.22). As secondary endpoints, no significant differences were seen for erlotinib *versus* chemotherapy for progression-free survival (HR 1.19; 95% CI, 0.97–1.46; $P = 0.0885$) or response rates (complete, 0% *versus* 0%; partial, 7.9% *versus* 6.3%). Erlotinib treatment demonstrated more dose modification or interruption (12.2% *versus* 3.3%) and treatment-related adverse events (AEs) (58.2% *versus* 40.8%), including rash and diarrhoea. Conversely, chemotherapy treatment showed more AEs leading to withdrawal/death (2.0%/1.5% *versus* 4.7%/5.2%) and serious AEs (10.2% *versus* 14.6%; including serious haematological events).

The study demonstrated that erlotinib is well tolerated and shows equivalent efficacy to chemotherapy in the second-line treatment of patients with advanced non-small-cell lung cancer (NSCLC), but with less toxicity.

Gefitinib

Gefitinib is targeted against tyrosine kinase activity on the EGF-R pathway.

During the phase II dose finding studies (IDEAL studies 1 and 2) gefitinib showed activity as monotherapy in patients with advanced NSCLC who had received prior chemotherapy, with overall response rates of 19% (IDEAL 1, Asian-European trial) [49] and 10% (IDEAL 2, US trial) [50]. These phase II studies were instrumental in gaining marketing approval in Japan and the USA. However, tumour analyses from these studies already raised some issues in identifying the patients who would be most likely to benefit.

In 2003, on the basis of encouraging phase II data, gefitinib received accelerated approval by the FDA for patients with locally advanced or metastatic NSCLC, after failure of both platinum-based and docetaxel chemotherapies. Nevertheless, no controlled phase III trial had demonstrated gefitinib efficacy, and accelerated approval regulations required the sponsor to conduct additional studies to confirm the activity and efficacy of gefitinib [8].

Subsequently, gefitinib was compared with placebo in the ISEL phase III trial, for patients with advanced NSCLC who had received one or two regimens of chemotherapy and who were refractory to or intolerant of their latest chemotherapy regimen [51].

In this study, 1,692 patients were randomly assigned in a 2:1 ratio to receive either gefitinib (orally, 250 mg daily) or placebo, plus best supportive care.

Overall survival (primary end-point) did not differ significantly between the groups, neither in the overall population nor among the 812 patients with adenocarcinoma. Because of these negative results, the conditions for gefitinib approval have been restricted, and the drug was relabeled by the FDA for use in patients already receiving it and obtaining a clinical

benefit [52]. Gefitinib is not presently available in the USA, Canada, or most European countries, but it remains approved in Asian countries including India, Japan, and China.

To demonstrate non-inferiority of gefitinib vs. mono-chemotherapy as second-line treatment required a much larger international study; the INTEREST study [53]. This open-label randomised phase III study recruited 1,466 patients (79% non-Asian, 21% of Asian ethnic origin) in progression after one or two chemotherapy regimens and randomised to docetaxel or gefitinib; it demonstrated that gefitinib was non-inferior in overall survival (593 vs. 576 events; HR 1.020, 96% CI 0.905–1.150) and similar in tumour response and PFS to docetaxel (median survival 7.6 months vs. 8.0 months).

The IPASS (Iressa Pan-ASia Study) randomised phase III trial compared gefitinib with carboplatin plus paclitaxel in 1217 Asian patients with advanced NSCLC [54].

Patients were selected according to clinical factors (adenocarcinoma and either never smokers or former light smokers). Gefitinib demonstrated superiority compared to carboplatin and paclitaxel (HR for PFS 0.74, CI 0.65–0.85, $P < 0.0001$). Gefitinib was significantly better than chemotherapy in terms of PFS in patients with *EGFR*-mutated tumours (HR for PFS 0.48, CI 0.36–0.64, $P < 0.0001$), whereas chemotherapy was significantly better in *EGFR* wild-type patients (HR for PFS 2.85, CI 2.05–3.98, $P < 0.0001$).

The analysis of OS according to mutational status, based on a smaller number of events, showed a HR for death with gefitinib of 0.78 (CI 0.50–1.20) in the subgroup with mutation and 1.38 (CI 0.92–2.09) in the subgroup without mutation. In July 2009, the EMEA granted marketing authorisation for gefitinib for the treatment of locally advanced or metastatic NSCLC with sensitising mutations of the *EGFR* gene, across all lines of therapy.

Recently a meta-analysis [55] compared efficacy of gefitinib (250 mg/day) and docetaxel (75 mg/m^2) using appropriate analysis populations from INTEREST [53] (1,466 patients randomised), V-15-32 [56], ISTANA [57] and SIGN [58]. Results were consistent with those of the individual studies. Given the similar/superior efficacy demonstrated by gefitinib, its favourable tolerability profile, quality of life benefits and oral administration, gefitinib has a favourable benefit–risk profile compared with docetaxel in a broad pre-treated advanced NSCLC patient population.

Clinical and molecular predictors of response

Regarding erlotinib there is some tendency to consider that it is only effective in certain subgroups of patients, such as women or Asians, or among patients with adenocarcinoma. Analysis of data from subgroups included in the BR.21 trial shows that overall survival is similar among women and men (HR 0.8 for both populations) [43]. Likewise, survival is similar among patients with adenocarcinoma and epidermoid carcinoma (HR 0.7 and 0.67, respectively).

When comparing Asian patients with other ethnicities, results are similar (HR 0.6 and 0.8, respectively). A most important group is that of male smokers with epidermoid carcinoma. In this population, HR in the erlotinib group (n = 100) is 0.66, and median survival was 5.5 months, as compared to 3.4 months in the placebo group (n = 57) [59]. Dermatologic toxicities are the most common adverse events associated with EGFR inhibitors, occurring in >50% of patients who receive treatment. The rash is dose dependent [60].

EGFR expression determined by immunohistochemistry (IHC) has been the first biological marker to be investigated as a possible molecular predictor of response to treatment with TKIs. Expression levels did not correlate with survival, stage, age, gender, or smoking history [61].

In 2006 Miller [62] published data from a prospective phase II trial about patients with bronchioloalveolar cell carcinoma (BAC). Gene amplification in combination with *EGFR* mutation (exon 19, 21) was shown to a strong predictor of response to erlotinib. Patients with both *EGFR* activating mutations and gene amplification had a 90% response rate and a median OS of 35 months.

In the BR.21 study, EGFR expression in the erlotinib-treated group was associated with a better response without a survival advantage [63]. Thus EGFR expression by IHC alone does not seem to be useful in predicting survival after erlotinib therapy. The FISH analysis from BR.21, however, did show a striking benefit in survival for the *EGFR* FISH-positive patients *versus* the FISH-negative patients ($P = 0.002$).

It has been argued that only patients with certain specific mutations respond to erlotinib. Somatic mutations in the *EGFR* gene are most frequently detected in a subpopulation of NSCLC patients with characteristics associated with a better treatment outcome, including adenocarcinomas histology and, in particular, bronchioloalveolar carcinoma, non-smokers, patients of Asian ethnicity and females [64].

In the BR.21 mutational analysis study, 40 of 177 (23%) samples were positive for mutations in exons

18–21 [63]. *EGFR* mutations were found at varying levels in the following subgroups: males (22%), females (24%), Asians (50%), non-Asians (21%), never smokers (31%), and adenocarcinoma (28%). In this trial, surprisingly the presence of mutations did not correlate with response or survival even in patients with classic exon 19 or 21 mutations. There was a trend towards better response rate in those with mutations, but not of statistical significance.

Zhu [64] evaluated the effect of *KRAS* and epidermal growth factor receptor (*EGFR*) genotype on the response to erlotinib treatment in the BR.21, placebo-controlled trial. Significant survival benefit from erlotinib therapy was observed for patients with wild-type *KRAS* (HR 0.69, $P = 0.03$) and *EGFR* FISH positivity (HR 0.43, $P = 0.004$) but not for patients with mutant *KRAS* (HR 1.67, $P = 0.31$), wild-type *EGFR* (HR 0.74, $P = 0.09$), mutant *EGFR* (HR 0.55, $P = 0.12$), and *EGFR* FISH negativity (HR 0.80, $P = 0.35$). In multivariate analysis, only *EGFR* FISH-positive status was prognostic for poorer survival ($P = 0.025$) and predictive of differential survival benefit from erlotinib ($P = 0.005$).

Regarding gefitinib, in 2006 Hirsch [65] analysed ISEL tumour biopsy samples to examine relationships between biomarkers and clinical outcome after gefitinib treatment in a placebo-controlled setting. High *EGFR* gene copy number was a predictor of a gefitinib-related effect on survival (HR 0.61 for high copy number and HR 1.16 for low copy number; comparison of high *versus* low copy number HR, $P = 0.045$). EGFR protein expression was also related to clinical outcome (HR for positive, 0.77; HR for negative, 1.57; comparison of high *versus* low protein expression HR, $P = 0.049$). Patients with *EGFR* mutations had higher response rates than patients without *EGFR* mutations (37.5% *versus* 2.6%).

In the INTEREST trial [53] the efficacy was irrespective of the patients' EGF-R protein expression (N = 380), EGF-R gene mutation (N = 297), or K-RAS gene mutation status (N = 275). The result for gene copy number (N = 374) was unexpected; previous work had suggested that it may be predictive for EGF-R-TKI efficacy; yet there was no difference to the docetaxel group.

In 2010 Douillard prospectively analysed available tumour biopsies to investigate the relationship between biomarkers and clinical outcomes [66]. For all biomarker subgroups analysed, survival was similar for gefitinib and docetaxel, with no statistically significant differences between treatments and no significant treatment by biomarker status interaction tests. *EGFR* mutation-positive patients had longer PFS (HR 0.16; 95% CI, 0.05–0.49; $P = 0.001$) and higher ORR (42.1% *versus* 21.1%; $P = 0.04$), and patients with high *EGFR* copy number had higher ORR (13.0% *versus* 7.4%; $P = 0.04$) with gefitinib *versus* docetaxel.

These biomarkers do not appear to be predictive factors for differential survival between gefitinib and docetaxel in this setting of previously treated patients.

Second line after maintenance treatment

The efficacy of pemetrexed as maintenance treatment was tested in a randomised trial [67,68] enrolling patients with advanced NSCLC without progression after four cycles of platinum-based chemotherapy (cisplatin or carboplatin plus gemcitabine or docetaxel or paclitaxel). In the overall study population, pemetrexed was significantly better than placebo both in terms of PFS (median 4.0 *versus* 2.0 months; HR 0.60, CI 0.49–0.73, $P < 0.00001$) and OS (median 13.4 *versus* 10.6 months; HR 0.79, CI 0.65–0.95, $P = 0.012$). Treatment with pemetrexed was well tolerated, without treatment-related deaths and with few severe adverse events. These results were considered by the panelists as interesting evidence, supporting a potential role for pemetrexed in maintenance treatment of patients with advanced NSCLC of non-squamous histology.

In July 2009, both the FDA and the EMEA approved pemetrexed as maintenance therapy for metastatic NSCLC, specifically in patients with non-squamous histology whose disease has not progressed after platinum-based first-line chemotherapy.

The SATURN [48] randomised phase III study compared erlotinib with placebo as maintenance treatment for patients with non-progressive NSCLC after four cycles of first-line platinum-based chemotherapy. The study met its primary endpoint, showing a statistically significant advantage in PFS for patients receiving erlotinib (HR 0.71, CI 0.62–0.82, $P < 0.0001$). Patients receiving erlotinib had a significantly longer survival than those receiving placebo (12 *versus* 11 months; HR 0.81, $P = 0.009$). In March 2009, an application was submitted to both the EMEA and the FDA for the use of erlotinib as maintenance treatment of patients not progressing after first-line platinum-based chemotherapy of advanced NSCLC.

For patients not progressing at the end of first-line therapy, the opportunity of maintenance treatment with drugs approved for this use in clinical practice should be discussed with each patient on an individual basis. Of course, squamous tumours are not eligible for maintenance with pemetrexed. If there is disease

progression in these squamous patients, after maintenance with erlotinib, in the second line we use only docetaxel.

Maintenance for non-squamous tumours can be erlotinib or pemetrexed. On disease progression we use docetaxel, erlotinib or pemetrexed as long as it has not been used in the maintenance therapy.

Other not registered biological agents

In second line, novel targeted therapies based on specific molecular and biological characteristics of lung cancer have been tested as a new treatment paradigm but actually are yet experimental.

Vandetanib

Vandetanib is a multi-target TKI that selectively targets VEGF-R, EGF-R and RET tyrosine kinase activity. In the ZODIAC study [69] (Zactima in cOmbination with Docetaxel In non-smAll cell lung Cancer), patients with advanced or metastatic NSCLC were enrolled after failure of prior platinum-based chemotherapy. Patients were randomised to treatment with a standard dose of docetaxel and either placebo or 100 mg of vandetanib or 300 mg of vandetanib. The study met its primary objective of PFS prolongation. The 100 mg vandetanib + docetaxel treatment group demonstrated a reduction in the risk of disease progression over a given period of time by 36% compared to docetaxel alone (HR 0.64, 95% CI, 0.39–1.05, $P = 0.074$).

ZEAL [70] (Zactima Efficacy with Alimta in Lung cancer) is a randomised, double-blind, placebo-controlled phase III study evaluating the combination of vandetanib 100 mg with pemetrexed *versus* pemetrexed alone in pre-treated patients with locally advanced or metastatic NSCLC. The primary endpoint did not reach statistical significance in the study, despite median PFS of 11.9 weeks vs. 17.6 weeks in favour of the vandetanib-plus-pemetrexed arm (HR 0.86, $P = 0.108$).

In June 2009 the regulatory submission for the use of vandetanib in combination with chemotherapy in patients with advanced NSCLC was withdrawn from the FDA and the EMEA. The decision was based on an updated analysis that demonstrated no overall survival advantage when vandetanib was added to chemotherapy.

ZEST [71] (Zactima Efficacy Study *versus* Tarceva) trial is a Phase III randomised, double-blind, multicentre study to assess the efficacy of vandetanib 300 mg *versus* erlotinib 150 mg in pre-treated-patients with locally advanced or metastatic NSCLC. Again, the primary objective of demonstrating a statistically significant prolongation of PFS for vandetanib was not met in this study. In a pre-planned non-inferiority analysis, vandetanib was shown to have similar efficacy to erlotinib for PFS and OS.

m-TOR inhibitors

The mammalian target of rapamycin (mTOR) is a serine-threonine kinase that functions as a central regulator of multiple signalling pathways that control cell growth, division, metabolism, and angiogenesis. In a recently published phase II study [72] 85 previously pretreated (platinum-based chemotherapy alone [N = 42] or in combination with EGF-R inhibitors [N = 43]) patients with relapsed NSCLC received everolimus (10 mg/day) until progression or unacceptable toxicity. Overall response rates (primary objective) were 7.1% and 2.3%, respectively. Overall disease control rate was 47.1%, median PFS was 2.6 and 2.7 months, respectively.

Bevacizumab

There is interest in determining whether combining bevacizumab and erlotinib offers and additional benefit. A phase II study [73] evaluated the safety of combining bevacizumab with either CT (docetaxel or pemetrexed) or erlotinib and preliminary assessed these combinations *versus* CT alone, as measured by PFS. One-year survival rate was 57.4% for bevacizumab–erlotinib and 53.8% for bevacizumab–CT compared with 33.1% for CT alone.

The phase III [74] Bevacizumab plus Tarceva (BeTa) trial of erlotinib with or without bevacizumab in the second-line treatment of NSCLC patients did not reach its primary endpoint of a longer OS time (9.3 months, *versus* 9.2 months for erlotinib plus placebo; HR 0.97; 95% CI, 0.80–1.18; $P < 0.75$), although the combination resulted in doubled PFS time (3.4 months, *versus* 1.7 months for erlotinib *versus* placebo; HR 0.62; 95% CI, 0.52–0.75; $P < 0.0001$).

Sunitinib

Sunitinib is an oral, selective multi-targeted TKI with antiangiogenic and antitumor activities.

SUN1058 [75] is a phase II trial in which 132 patients with stage IIIB/IV NSCLC with $\leqslant 2$ prior treatments were randomised to receive sunitinib 37.5 mg/day as sunitinib + erlotinib 150 mg/day (SU+E) or placebo + erlotinib 150 mg/day (P+E). Median PFS was 12.3 weeks for SU+E *versus* 8.5 weeks for P+E (HR 0.945; 95% CI, 0.601–1.488). Median OS was

8.2 months for SU+E *versus* 7.6 months for P+E. The toxicity profile was acceptable.

SUN1087 [76] is a multicentre, randomised, double-blind phase III study of SU+E, again on a CCD schedule, *versus* E+P. This study did not demonstrate an increase in OS (median OS, 9 *versus* 8.5 months; HR 0.922, 95% CI, 0.797–1.067) but did demostrate a significant improvement in PFS (median PFS, 15.5 *versus* 8.7 weeks; HR 0.807, 95% CI, 0.695–0.937) for SU+E compared to P+E.

Sorafenib

In a phase II trial, sorafenib combined with erlotinib appeared to be effective against advanced NSCLC [77]. Previously treated patients patients received sorafenib 400 mg twice daily and erlotinib 150 mg daily in 28-day cycles. The ORR (primary endpoint) and DCR were 30.4% and 63%, respectively. The PFS and OS were 183 days and not-reached, respectively.

c-MET inhibitors

New agents targeted against the c-Met kinase receptor or its ligand are now in the clinic and have shown promising results in several diseases.

A phase II study [78] enrolled patients with advanced NSCLC previously treated, who were randomised to receive erlotinib at the 150 mg daily dose plus ARQ 197 360 mg twice daily (E+A) or erlotinib plus placebo. Median OS with E+A was 36.6 weeks, compared with 29.4 weeks for patients given E+P (HR 0.88; 95% CI, 0.60–1.3; $P = 0.52$). OS benefits were most pronounced in non-squamous histology (median OS, 43.1 *versus* 29.4 weeks; HR 0.58; $P < 0.05$).

Proteasome inhibitors

A phase II trial [79] has been performed to determine the efficacy and safety of erlotinib alone (arm A) or erlotinib plus bortezomib (arm B) in patients with relapsed or refractory, locally advanced or metastatic NSCLC. The study was halted at the planned interim analysis due to insufficient clinical activity in arm B.

Conclusions

Today, second-line treatment can be considered a standard of care. In the USA and Europe, the current options for the second- and third-line treatment of advanced non-small cell lung cancer (NSCLC) are cytotoxic drugs (pemetrexed, docetaxel) and targeted agents (erlotinib, gefitinib).

This necessitates the implementation of a rational treatment plan for first-, second- and third-line therapy. Treatment decisions should be guided by evidence from large-scale studies with well-defined, standard patient populations [80].

In the meantime, we propose the following treatment algorithm of advanced NSCLC:

- In second-line setting for non-squamous tumours the best choice could be either docetaxel or pemetrexed or an EGFR-tyrosine kinase inhibitor, depending on the drug first used and the presence of *EGFR* mutations.
- Patients with squamous tumours could receive erlotinib or docetaxel depending on the drug used in the first-line setting.
- Finally, only erlotinib may represent an optimal third-line option in tumours of any histology, except if previously used.

For patients not progressing at the end of first-line therapy, the opportunity of maintenance treatment with drugs approved for this use in clinical practice should be discussed with each patient on an individual basis.

Conflict of interest statement

F. de Marinis: Honoraria as speaker bureau and advisory board member for Roche and Lilly. S. Ricciardi: no conflict of interest.

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